

AMENDMENTS TO THE CLAIMS

This listing of the claims will replace all prior versions, and listings, of claims in the application:

1. (Original): A purified thrombospondin fragment that has been extracted from a bodily fluid, said fragment being one within a molecular weight range selected from the group consisting of 80 to 110 kDa, 40 to 60 kDa, and 20 to 35 kDa, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

Claims 2-5 (canceled).

6. (Original): A purified and/or synthetic thrombospondin fragment or portion thereof, said fragment selected from the group comprising one that starts between amino acyl residues I-165 and V-263, inclusive, and ends between amino acyl residues K-412 and I-530, inclusive;

one that starts between amino acyl residues I-165 and V-263, inclusive, and ends between amino acyl residues I-530 and R-733, inclusive;

and one that starts between amino acyl residues I-165 and V-263, inclusive, and ends between amino acyl residues R-792 and Y-982, inclusive, said portion being at least 4 amino acyl acids in length.

7. (Original): A purified and/or synthetic thrombospondin fragment or portion thereof, selected from the group comprising one that starts between amino acyl residues N-230 and G-253 inclusive, and ends between amino acyl residues V-400 and S-428, inclusive;

one that starts between amino acyl residues N-230 and G-253, inclusive, and ends between amino acyl residues D-527 and S-551, inclusive;

and one that starts between amino acyl residues N-230 and G-253, inclusive, and ends between amino acyl residues G-787 and V-811, inclusive, said portion being at least 4 amino acyl acids in length.

8. (Original): A purified thrombospondin fragment, the molecular weight of said fragment not exceeding 100 kDa, said fragment comprising at least 4 contiguous amino acyl residues from the thrombospondin sequence, wherein the amino acid sequence of the fragment is

limited to the group consisting of a fragment that is outside of a thrombospondin region defined in Claim 6 and a fragment that is outside of a thrombospondin region defined in Claim 7.

9. (Original): A purified and/or synthetic thrombospondin fragment, the molecular weight of said fragment not exceeding 110 kDa, said fragment being at least 4 contiguous amino acyl residues in length, and wherein the fragment comprises a domain or a part thereof within the protease-resistant core of thrombospondin, said domain being selected from the group consisting of a domain of inter-chain disulfide bonds, an oligomerization domain, a procollagen-like domain, a type 1 repeat, a type 2 repeat, and a type 3 repeat.

10. (Original): A purified and/or synthetic thrombospondin fragment, the molecular weight of said fragment not exceeding 110 kDa, said fragment being at least 4 contiguous amino acyl residues in length, and wherein the fragment comprises an amino acid sequence selected from the group consisting of TEENKE (SEQ ID NO: 1), CLQDSIRKVTEENKE (SEQ ID NO: 2), LQDSIRKVTEENKE (SEQ ID NO: 3), EGEARE (SEQ ID NO: 4), PQMNGKPCEGEARE (SEQ ID NO: 5), EDTDLD (SEQ ID NO: 6), YAGNGIICGEDTDLD (SEQ ID NO: 7), CNSPSPQMNGKPCEGEAR (SEQ ID NO: 8), RKVTEENKELANELRRP (SEQ ID NO: 9), CRKVTEENKELANELRRP (SEQ ID NO: 10), PQMNGKPCEGEAR (SEQ ID NO: 11), CEGEAR (SEQ ID NO: 12), RKVTEENKE (SEQ ID NO: 13), TERDDD (SEQ ID NO: 24), DFSGTFFINTERDDD (SEQ ID NO: 25), ERKDHS (SEQ ID NO: 26), TRGTLLALERKDHS (SEQ ID NO: 27), CTRGTLLALERKDHS (SEQ ID NO: 28), DDKFQD (SEQ ID NO: 29), ANLIPPVPDDKFQD (SEQ ID NO: 30), CANLIPPVPDDKFQD (SEQ ID NO: 31), DCEKME (SEQ ID NO: 32), EDRAQLYIDCEKMEN (SEQ ID NO: 33), CGTNRIPESGGDNSVFD (SEQ ID NO: 34), NRIPESGGDNSVFD (SEQ ID NO: 35), GWKDFTAYRWRLSHRPKTG (SEQ ID NO: 36), CGWKDFTAYRWRLSHRPKTG (SEQ ID NO: 37), DDDDNDKIPDDRDNC (SEQ ID NO: 14), DDDDNDKIPDDRDNC[NH₂] (SEQ ID NO: 15), DDDDNDK (SEQ ID NO: 16), NLPNSGQEDYDKDG (SEQ ID NO: 17), CNLPNSGQEDYDKDG (SEQ ID NO: 18), EDYDKD (SEQ ID NO: 19), CPYNHNPDQADTDNNGEGD (SEQ ID NO: 20), CRLVPNPDQKDSGD (SEQ ID NO: 21), DQKDSGD (SEQ ID NO: 22), CPYVPNANQADHDKDGKGDA (SEQ ID NO: 23), and a portion of such an amino acid sequence.

11. (Original): A purified and/or synthetic thrombospondin fragment, the molecular weight of said fragment not exceeding 110 kDa, said fragment being at least 4 contiguous amino acyl residues in length, and wherein the fragment comprises a portion of a collagen type V binding domain.

12. (Original): A purified and/or synthetic thrombospondin fragment, the molecular weight of said fragment not exceeding 110 kDa, said fragment being at least 4 contiguous amino acyl residues in length, and wherein the fragment comprises an epitope for binding the TSP Ab-4 antibody.

13. (Original): A purified and/or synthetic thrombospondin fragment, the molecular weight of said fragment not exceeding 110 kDa, said fragment being at least 4 contiguous amino acyl residues in length, and wherein the fragment does not comprise a fibrinogen-binding region selected from the group consisting of (1) a fibrinogen-binding domain within a 210-kDa fragment of TSP, where said 210-kDa fragment is composed of three 70-kDa fragments that contain the region of interchain disulfide bonds, the procollagen homology region, and the type 1 and type 2 repeats, (2) a fibrinogen-binding region in the amino-terminal domain of thrombospondin, (3) a fibrinogen-binding region in an 18-kDa amino-terminal heparin-binding domain of thrombospondin, and (4) a region corresponding to synthetic peptide N12/I encompassing amino acid residues 151-164 (I-151 to P-164) of the N-terminal domain of thrombospondin-1.

Claims 14-56 (canceled).

57. (Currently amended): An antibody produced by the method of Claim ~~[[54]]~~ 165.

58. (Currently amended): A cell line producing the monoclonal antibodies of Claim ~~[[56]]~~ 166.

59. (Canceled).

60. (Currently amended): A method of producing a peptide or non-peptide binding agent against a thrombospondin fragment of ~~Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, a Claim 1, 6, 7, 8, 9, 10, 11, 12 or 13, a~~ fragment portion of Claim 6 or Claim 7, or epitope therein, said method comprising the steps of

1) a generating step (random, semi-random, directed, combinatorial, and/or other) to generate

large numbers (>100) of diverse peptides and/or non-peptides;

- 2) a selection step to identify within this large number those peptides and/or non-peptides that bind to the thrombospondin fragment, fragment portion, and/or an epitope therein; and
- 3) optionally an improvement step for improving the peptide or non-peptide binding agent to achieve better affinity and/or specificity.

Claims 61-63 (canceled).

64. (Original): A cell line capable of producing a binding agent produced by the method of Claim 60.

65. (Canceled).

66. (Currently amended): A kit for the determination of the presence of, and/or the amount of, and/or the concentration of, a thrombospondin fragment in a material taken or gathered from an organism, said kit comprising a thrombospondin fragment of ~~Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13~~ Claims 1, 6, 7, 8, 9, 10, 11, 12 or 13 or a fragment portion of Claim 6 or Claim 7.

67. (Original): A kit for the determination of the presence of, and/or the amount of, and/or the concentration of, one or more thrombospondin fragments in a material taken or gathered from an organism, said kit comprising a binding agent capable of binding said one or more of said fragments.

Claims 68-77 (canceled).

78. (Original): A kit for the determination of the presence of, and/or the amount of, and/or the concentration of, one or more thrombospondin fragments in a material taken or gathered from an organism, said kit comprising a binding agent that will react with thrombospondin but not with the fragment or fragments of interest.

Claims 79-92 (canceled).

93. (Original): A kit for the determination of the presence of, and/or the amount of, thrombospondin fragments in a material taken or gathered from an organism, said kit comprising an antibody that will react thrombospondin fragments of interest but not with thrombospondin.

Claims 94-109 (canceled).

110. (Currently amended): A method to detect the presence and/or clinical course of a

neoplastic disease in an individual, wherein the method comprises the steps of:

- (1) measuring the individual's plasma level of a thrombospondin fragment or fragments;
- (2) utilizing the result of step (1) in a diagnosis as to whether the individual has a neoplastic disease; said fragment or fragments being a fragment of ~~Claims 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12 and/or~~ Claims 1, 6, 7, 9, 10, 11, 12 and/or 13, and/or comprising an epitope therein.

Claims 111-145 (canceled).

146. (Currently amended): A monoclonal antibody produced by the method of Claim [[145]] 167.

147. (Original): A cell line producing a monoclonal antibody of Claim 146.

148. (Currently amended): A polyclonal antibody preparation produced by the method of Claim [[145]] 167.

149. (Original): A method of producing a binding agent against a thrombospondin fragment, said fragment at least 6 amino acyl residues in length, said method comprising binding a phage to said thrombospondin fragment.

Claims 150-156 (canceled).

157. (Canceled).

158. (Original): A purified and/or synthetic thrombospondin fragment or portion thereof, said fragment selected from the group comprising one that starts between amino acyl residues I-165 and V-263, inclusive, and ends between amino acyl residues K-412 and I-530, inclusive;

one that starts between amino acyl residues I-165 and V-263, inclusive, and ends between amino acyl residues I-530 and R-733, inclusive;

and one that starts between amino acyl residues I-165 and V-263, inclusive, and ends between amino acyl residues R-733 and Y-982, inclusive, said portion being at least 6 amino acyl acids in length.

Claims 159-164 (canceled).

165. (New): A method of producing antibodies against a thrombospondin fragment of Claims 1, 6, 7, 8, 9, 10, 11, 12 or 13 or a fragment portion of Claim 6 or Claim 7 said method comprising administering said fragment, fragment portion or immunogenic portion thereof to an organism capable of producing antibodies.

166. (New): A method of Claim 165 wherein monoclonal antibodies are produced.

167. (New): A method of producing antibodies against a thrombospondin fragment, said fragment at least 6 amino acyl residues in length, said method comprising administering said fragment to an organism capable of producing antibodies.